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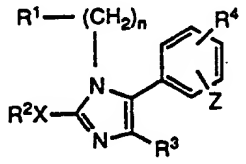
(54) Title: SUBSTITUTED 5-ARYL IMIDAZOLES



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(57) Abstract

Angiotensin II receptor antagonists having formula (1) which are useful in regulating hypertension and in the treatment of congestive heart failure, renal failure, and glaucoma, pharmaceutical compositions including these antagonists, and methods of using these compounds to produce angiontensin II receptor antagonism in mammals.

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SUBSTITUTED 5-ARYL IMIDAZOLES

The present invention relates to new substituted 5-aryl imidazoles which are angiotensin II receptor antagonists and are useful in regulating hypertension induced or exacerbated by angiotensin II, and in the treatment of congestive heart failure, renal failure, and glaucoma. This invention also relates to pharmaceutical compositions containing these compounds and methods for using these compounds as antagonists of angiotensin II, as antihypertensive agents and as agents for treating congestive heart failure, renal failure, and glaucoma.

BACKGROUND OF THE INVENTION

The class of peptide pressor hormone known as angiotensin is responsible for a vasopressor action that is implicated in the etiology of hypertension in man. Inappropriate activity of the renin-angiotensin systems appears to be a key element in essential hypertension, congestive heart failure and in some forms of renal disease. In addition to a direct action on arteries and arterioles, angiotensin II (AII), being one of the most

potent endogenous vasoconstrictors known, exerts stimulation on the release of aldosterone from the adrenal cortex. Therefore, the renin-angiotensin system, by virtue of its participation in the control of renal sodium handling, plays an important role in cardiovascular hemeostasis.

Interruption of the renin-angiotensin system with converting enzyme inhibitors, such as captopril, has proved to be clinically useful in the treatment of hypertension and congestive heart failure (Abrams, W.B., et al., (1984), Federation Proc., 43, 1314). The most direct approach towards inhibition of the renin-angiotensin system would block the action of AII at the receptor. Compelling evidence suggests that AII also contributes to renal vasoconstriction and sodium retention that is characteristic of a number of disorders such as heart failure, cirrhosis and complications of pregnancy (Hollenberg, N.K., (1984), J. Cardiovas. Pharmacol., 6, S176). In addition, recent animal studies suggest that inhibition of the renin-angiotensin system may be beneficial in halting or slowing the progression of chronic renal failure (Anderson, S., et al., (1985), J. Clin. Invest., 76, 612). Also, a recent patent application (South African Patent Application No. 87/01,653) claims that AII antagonists are useful as agents for reducing and controlling elevated intraocular pressure, especially glaucoma, in mammals.

The compounds of this invention inhibit, block and antagonize the action of the hormone AII, and are therefore useful in regulating and moderating angiotensin induced hypertension, congestive heart failure, renal failure and other disorders attributed to the actions of AII. When compounds of this invention are administered to mammals, the elevated blood pressure due to AII is reduced and other manifestations based on AII intercession are minimized and controlled.

Compounds of this invention are also expected to exhibit diuretic activity.

Recognition of the importance of blocking and inhibiting the actions of AII has stimulated other efforts to synthesize antagonists of AII. The following references have disclosed imidazole derivatives which are described as having AII blocking activity and useful as hypotensive agents.

Furukawa et al., U.S. Patent 4,340,598 discloses imidazol-5-yl-acetic acids and imidazol-5-yl-propanoic acids. Specifically, the discloser includes 1-benzyl-2-n-butyl-5-chloroimidazole-4-acetic acid and 1-benzyl-2-phenyl-5-chloroimidazole-4-propanoic acid.

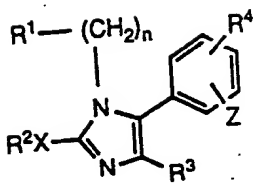
Furukawa, et al., U.S. Patent 4,355,040 discloses substituted imidazole-5-acetic acid derivatives. A compound specifically disclosed is 1-(2-chlorobenzyl)-2-n-butyl-4-chloroimidazole-5-acetic acid.

Furukawa, et al., in EP 103 647 discloses substituted 1-benzyl-2-phenyl-4-chloro-imidazol-5-yl-acetic acid derivatives. Specifically, the disclosure includes 4-chloro-1-(4-methoxy-3-methylbenzy)-2-phenyl-imidazole-5-acetic acid.

Carini, et al., in EP 253 310 discloses certain 1-aralkyl-imidazoles. Examples include 2-n-butyl-5-chloro-1-(4-nitrobenzyl)imidazole-4-acetic acid and methyl 1-[2'-carboxybiphenyl-4-yl-methyl]-2-n-butyl-4-chloroimidazole-5-carboxylate.

DESCRIPTION OF THE INVENTION

The compounds of the present invention that are blockers of angiotensin II receptors are represented by the following Formula (I):



(I)

in which:

R^1 is adamantylmethyl, or phenyl, biphenyl, or naphthyl, with each aryl group being unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_1-C_6alkyl, nitro, CO_2R^5, C_1-C_6alkoxy, hydroxy, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, tetrazol-5-yl, SO_2NHR^5, $NHSO_2R^5$, SO_3H, $PO(OR^5)_2$, $CONR^5R^5$, CN, NR^5R^5, NR^5COH, NR^5COC_1-C_6alkyl, $NR^5CON(R^5)_2$, NR^5COW, SO_2W, or W;

R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, $(CH_2)_{0-8}C_{3-6}$cycloalkyl, or $(CH_2)_{0-8}$phenyl unsubstituted or substituted by one to three substituents selected from C_1-C_6alkyl, nitro, Cl, Br, F, I, hydroxy, C_1-C_6alkoxy, NR^5R^5, CO_2R^5, CN, $CONR^5R^5$, W, tetrazol-5-yl, NR^5COH, NR^5COC_1-C_6alkyl, NR^5COW, SO_2W, SO_2C_1-C_6alkyl, or SC_1-C_6alkyl;

X is a single bond, S, NR^5, or O;

n is 0-4;

R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, C_1-C_6alkyl, NR^5R^5, CO_2R^5, $CONR^5R^5$, NO_2, CN, phenyl, or W;

R^4 is CO_2R^5, $CONR^5R^5$, or tetrazol-5-yl;

Z is hydrogen, Cl, Br, F, I, C_1-C_6alkyl, C_1-C_6alkoxy, hydroxy, CN, NO_2, CO_2R^5, COR^5R^5, W, phenyl-Y-, naphthyl-Y-, thienyl-Y-, furyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, thiazolyl-Y-, tetrazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, or isoxazolyl-Y-, with each aryl or heteroaryl group being unsubstituted or

substituted by C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CO_2R^5, hydroxy, NO_2, CN, $CONR^5R^5$, or W;

Y is a single bond or C_1-C_6alkyl, which is straight or branched;

W is C_mF_{2m+1}, wherein m is 1-4,; and

each R^5 independently is H or C_1-C_6alkyl;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of the invention are represented by Formula (I) wherein:

R^1 is phenyl unsubstituted or substitiuted by one to three substituents selected from chloro, fluoro, nitro, methyl, trifluoromethyl, methoxy, hydroxy, sulfonamido, sulfamyl, cyano, carboxy, carboC_{1-6}alkoxy, carbamoyl, or tetrazol-5-yl;

R^2 is C_2-C_8alkyl;

X is a single bond or S;

R^3 is hydrogen, chloro, fluoro, or trifluoromethyl; and

Z is hydrogen, Cl, Br, F, I, C_1-C_4akyl, C_1-C_4alkoxy, hydroxy, CO_2H, or CO_2C_1-C_4alkyl;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms alkyl, alkenyl, alkoxy, and alkynyl mean carbon chains which are branched or unbranched with the length of the chain determined by the discriptor preceding the term.

Particular compounds of the invention include, but are not limited to, the following:

4-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid,

3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid, and

2-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid;

or a pharmaceutically acceptable salt thereof.

The invention also relates to pharmaceutical compositions comprising a pharmaceutical carrier and an effective amount of a compound of Formula (I).

Also included in the present invention are methods for antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I). Methods of producing antihypertensive activity and methods of treating congestive heart failure, glaucoma, and renal failure by administering these compounds are also included in this invention.

The compounds of this invention are prepared by procedures described herein and illustrated by the examples. Reagents, protecting groups and functionality on the imidazole and other fragments of the molecule must be consistent with the proposed chemical transformations. Steps in the synthesis must be compatible with the functional groups and the protecting groups on the imidazole and other parts of the molecule.

The starting materials, 2-R^2X-imidazole, are known to the art (J. Org. Chem. 45:4038, 1980) or are synthesized by known procedures. For example, imidazole is converted to 2-n-butylimidazole by reacting imidazole with triethylorthoformate and p-toluenesulfonic acid to give 1-diethoxyorthoamide imidazole and then treating with n-butyl lithium to give the 2-lithium derivative of the orthoamide and alkylating with n-butyl iodide in a suitable solvent, such as tetrahydrofuran (THF).

The following procedure is useful for the preparation of compounds of Formula (I) compounds particularly where R^1 is 2-chlorophenyl or 4-carboxyphenyl, n is one, R^2 is n-butyl or n-propyl, X is a single bond or S, R^3 is hydrogen, R^4 is CO_2H, and Z hydr gen.

The 2-R^2X-imidazole starting materials are reacted with trimethylsilylethoxymethyl(SEM) chloride to give 1-(trimethylsilyl)ethoxymethyl-2-R^2X-imidazole. The reaction is carried out, for example, in the presence of sodium hydride in a solvent such as dimethylformamide. The 5-tributyltin derivatives are prepared by lithiation

with, for example, butyllithium in a suitable solvent, preferably diethyl ether, followed by treatment of the lithio imidazole derivative with a tributyltin halide, preferably tri-N-butyltin chloride, at -10°C to 35°C, preferably at 25°C. The 1-SEM-2-R^2X-5-tributyltin-imidazole is coupled with an appropriately substituted benzoic acid ester having a leaving group, such as a halide or a trifluoromethane-sulfonyloxy group, for example, methyl 4-trifluoromethane-sulfonyloxybenzoate, in the presence of a phosphine ligand such as bis(diphenylphosphino)propane, or triphenylphosphine and a palladium (II) compound, or preferably tetrakis-(triphenylphosphine)palladium (0), in a suitable solvent, such as dioxane, at a temperature of 50°C to 150°C, preferably at 100°C. The 1-SEM group is hydrolyzed with acid, for example, aqueous hydrochloric acid, in a suitable alcoholic solvent, such as methanol or ethanol. The 1-unsubstituted imidazole derivatives are converted to the 1-t-butoxycarbonyl (t-BOC) imidazoles with di-t-butyl dicarbonate (Hoppe-Seyler's Z. Physiol. Chem., (1976), 357, 1651). The t-BOC esters are alkylated and hydrolyzed with, for example, 2-chlorobenzyl-O-triflate in the presence of a suitable base, preferably diisopropylethylamine, in a suitable solvent, preferably methylene chloride, to afford the 1-(2-chlorophenyl)methylimidazole derivatives (esters). The Formula (I) ester compounds are hydrolyzed to the corresponding Formula (I) carboxylic acid compounds, 1-$R^1(CH_2)_n$-2-R^2X-5-benzoic acid-imidazoles, using base, such as potassium hydroxide, lithium hydroxide, or sodium hydroxide, in a suitable solvent system, such as aqueous alcohols or diglyme.

Compounds of Formula (I) in which the R^1 substituent is substituted by hydroxy or the Z group is hydroxy are formed from Formula (I) compounds in which the R^1 group is substituted by C_1-C_4alkoxy or the Z substituent is C_1-C_4alkoxy using an ether-cleaving

reagent, such as boron tribromide or hydrobromic acid.

Compounds of Formula (I) in which the R^1 substituent is substituted by carboxy or the Z group is carboxy are formed from Formula (I) compounds in which the R^1 group is substituted by CO_2C_1-C_4alkyl or the Z group is CO_2C_1-C_4alkyl using basic hydrolysis, such as aqueous sodium or potassium hydroxide in methanol or ethanol, or using acidic hydrolysis, such as aqueous hydrochloric acid.

Compounds of Formula (I) in which the R^1 substituent is substituted by a tetrazol-5-yl group or the Z group is tetrazol-5-yl are prepared from the corresponding carboxy compounds. Also, when the carboxylic acid functionality on the 5-benzoic acid group is converted to the tetrazol-5-yl substituent the following procedure is employed. Formula (I) acid compounds are reacted with a halogenating agent, such as thionyl chloride, in a suitable solvent, for example benzene, to give the corresponding acid halide compounds. The acid halides are then converted to primary amide compounds in a reaction with concentrated ammonia. Subsequent dehydration of the amides with oxalyl chloride/dimethylformamide in acetonitrile/ dimethylformamide yields the nitrile compounds, which are the immediate precursors to the Formula (I) tetrazole compounds. Tetrazole formation is accomplished by reacting the nitriles with azide, preferably aluminum azide prepared in situ by the reaction of sodium azide with aluminum chloride, in a suitable solvent, for example tetrahydrofuran to give Formula (I) tetrazole compounds.

Pharmaceutically acceptable acid addition salts of compounds of Formula (I) are formed with appropriate organic or inorganic acids by methods known in the art. For example, the base is reacted with a suitable inorganic or organic acid in an aqueous miscible solvent such as ethanol with isolation of the salt by removing

the solvent or in an aqueous immiscible solvent when the acid is soluble therein, such as ethyl ether or chloroform, with the desired salt separating directly or isolated by removing the solvent. Representative examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

Pharmaceutically acceptable base addition salts of compounds of Formula (I) in which a carboxy group is present are prepared by known methods from organic and inorganic bases, including nontoxic alkali metal and alkaline earth bases, for example, calcium, lithium, sodium, and potassium hydroxide; ammonium hydroxide, and nontoxic organic bases, such as triethylamine, butylamine, piperazine, meglumine, choline, diethanolamine, and tromethamine.

Angiotensin II antagonist activity of the compounds of Formula (I) is assessed by <u>in vitro</u> and <u>in vivo</u> methods. <u>In vitro</u> antagonist activity is determined by the ability of the compounds to compete with ^{125}I-angiotensin II for binding to vascular angiotensin II receptors and by their ability to antagonize the contractile response to angiotensin II in the isolated rabbit aorta. <u>In vivo</u> activity is evaluated by the efficacy of the compounds to inhibit the pressor response to exogenous angiotensin II in conscious rats and to lower blood pressure in a rat model of renin dependent hypertension.

<u>Binding</u>

The radioligand binding assay is a modification of a method previously described in detail (Gunther et al.,

Circ. Res. 47:278, 1980). A particular fraction from rat mesenteric arteries is incubated in Tris buffer with 80 pM of ^{125}I-angiotensin II with or without angiotensin II antagonists for 1 hour at 25°C. The incubation is terminated by rapid filtration and receptor bound ^{125}I-angiotensin II trapped on the filter is quantitated with a gamma counter. The potency of angiotensin II antagonists is expressed as the IC_{50} which is the concentration of antagonist needed to displace 50% of the total specifically bound angiotensin II. Exemplary of the IC_{50} of compounds of the invention is about 3.5 to about 17.5 μM.

Aorta

The ability of the compounds to antagonize angiotensin II induced vasoconstriction is examined in the rabbit aorta. Ring segments are cut from the rabbit thoracic aorta and suspended in organ baths containing physiological salt solution. The ring segments are mounted over metal supports and attached to force displacement transducers which are connected to a recorder. Cumulative concentration response curves to angiotensin II are performed in the absence of antagonist or following a 30-minute incubation with antagonist. Antagonist disassociation constants (K_B) are calculated by the dose ratio method using the mean effective concentrations. Exemplary of the K_B of compounds of the invention is about 23.5 to about 100 μM.

Inhibition of pressor response to angiotensin II in conscious rats

Rats are prepared with indwelling femoral arterial and venous catheters and a stomach tube (Gellai et al., Kidney Int. 15:419, 1979). Two to three days following surgery the rats are placed in a restrainer and blood pressure is continuously monitored from the arterial

catheter with a pressure transducer and recorded on a polygraph. The change in mean arterial pressure in response to intravenous injections of 250 mg/kg angiotensin II is compared at various time points prior to and following the administration of the compounds intravenously or orally at doses of 0.1 to 300 mg/kg. The dose of compound needed to produce 50% inhibition of the control response to angiotensin II (IC_{50}) is used to estimate the potency of the compounds.

Antihypertensive activity

The antihypertensive activity of the compounds is measured by their ability to reduce mean arterial pressure in conscious rats made renin-dependent hypertensive by ligation of the left renal artery (Cangiano et al., J. Pharmacol. Exp. Ther. 208:310, 1979). Renal artery ligated rats are prepared with indwelling catheters as described above. Seven to eight days following renal artery ligation, the time at which plasma renin levels are highest, the conscious rats are placed in restrainers and mean arterial pressure is continuously recorded prior to and following the administration of the compounds intravenously or orally. The dose of compound needed to reduce mean arterial pressure by 30 mm Hg (IC_{30}) is used as an estimate of potency.

The intraocular pressure lowering effects employed in this invention may be measured by the procedure described by Watkins, et al., J. Ocular Pharmacol., 1 (2):161-168 (1985).

The compounds of Formula (I) are incorporated into convenient dosage forms, such as injectable preparations, or for orally active compounds, capsules or tablets. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and

stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid, such as an ampoule, or an aqueous or nonaqueous liquid suspension.

For topical ophthalmolgic administration, the pharmaceutical compositions adapted include solutions, suspensions, ointments, and solid inserts. Typical pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, and water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting, and bodying agents, as for example, polyethylene glycols; antibacterial components, such as quarternary ammonium compounds; buffering ingredients, such as alkali metal chloride; antioxidants, such as sodium metabisulfite; and other conventional ingredients, such as sorbitan monolaurate.

Additionally, suitable ophthalmic vehicles may be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems.

The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral, parenteral, or topical products.

Doses of the compounds of Formula (I) in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity selected from the range of .01 - 200 mg/kg of active compound, preferably - 100 mg/kg. The selected dose is administered to a human patient in need of angiotensin II receptor antagonism from 1-6 times daily, orally, rectally, topically, by injection, or continuously by infusion. Oral dosage units for human administration preferably contain from 1 to 500 mg of active compound. Preferably, lower dosages are used for parenteral administration. Oral administration, at higher dosages, however, also can be used when safe and convenient for the patient. Topical formulations contain the active compound in an amount selected from 0.0001 to 0.1 (w/v%), preferably from 0.0001 to 0.01. As a topical dosage unit form, an amount of active compound from between 50 ng to 0.05 mg, preferably 50 ng to 5 µg, is applied to the human eye.

The method of this invention of antagonizing angiotensin II receptors in mammals, including humans, comprises administering to a subject in need of such antagonism an effective amount of a compound of Formula (I). The method of this invention of producing antihypertensive activity and the method of treating congestive heart failure, glaucoma, and renal failure comprise administering a compound of Formula (I) to a subject in need thereof an effective amount to produce said activity.

Contemplated equivalents of Formula (I) compounds are compounds otherwise corresponding thereto wherein

substituents have been added to any of the unsubstituted positions of the Formula (I) compounds provided such compounds have the pharmaceutical utility of Formula (I) compounds.

The following examples illustrate preparation of compounds and pharmaceutical compositions of this invention. The examples are not intended to limit the scope of this invention as defined hereinabove and as claimed below.

Example 1

3-[2-n-Butyl-1-[(2-chlorophenylmethyl)-1H-imidazol-5-yl]benzoic Acid

(i) 2-n-butyl-1-(trimethylsilyl)ethoxymethyl-imidazole

Hexane-washed 80% sodium hydride (1.45 g, 0.0483 mol) in dimethylformamide (80 mL) under argon was treated with a solution of 2-n-butylimidazole (5.45 g, 0.0439 mol) in dimethylformamide (14 mL) dropwise at 25°C and the reaction was stirred an additional hour. Then 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) (7.68 g, 0.0461 mol) was added, the mixture was stirred for 18 hours at ambient temperature and then partitioned between ice water and ethyl acetate. The washed, dried, concentrated organic solution was chromatographed over silica gel with 1:1 hexane in ethyl acetate to yield 10.8 g (96%) of 2-n-butyl-1-(trimethylsilyl)ethoxy-methylimidazole.

(ii) 2-n-butyl-5-tributyltin-1-(trimethylsilyl)-ethoxymethylimidazole

A solution of 2-n-butyl-1-SEM imidazole (prepared above) (6.37 g, 0.025 mol) in ethyl ether (125 mL) was treated dropwise with n-butyl lithium (0.0255 mol, 10.2

mL of 2.5 M in hexane) under argon at room temperature. After being stirred for an additional 45 minutes, tributyltin chloride (8.83 g, 7.4 mL, 0.026 mol) was added dropwise. The suspension was stirred overnight, saturated ammonium chloride solution was added and the ether layer was separated, washed with brine, dried over sodium sulfate, concentrated and flash chromatographed over silica gel with 3:1 hexane/ethyl acetate to provide 11.3 g (83%) of 2-n-butyl-5-tributyltin-1-(trimethylsilyl)ethoxymethylimidazole.

(iii) methyl 3-trifluoromethanesulfonyloxybenzoate

To a solution of methyl 3-hydroxybenzoate (1.73 g, 11.3 mmol), 4-dimethylaminopryridine (215 mg, 1.74 mmol), and 2,6-lutidine (2.0 mL, 16.6 mmol) in 60 mL of methylene chloride at -30°C was added trifluoromethanesulfonic anhydride (2.8 mL, 16.6 mmol). After stirring the reaction mixture for 10 min at -30°C, the cooling bath was removed and the reaction was stirred at ambient temperature for 4 hours. Saturated aqueous ammonium chloride solution was then added, the layers were separated and the aqueous layer was back extracted twice with methylene chloride. The combined organic extracts were dried with sodium sulfate and the methylene chloride was removed in vacuo. The residue was dissolved in ethyl acetate and washed with water, 10% aqueous hydrochloric acid solution, saturated sodium bicarbonate solution and brine. The organic extract was dried with magnesium sulfate and the solvent was removed in vacuo. The crude product was flash chromatographed over silica gel eluting with 1:1 diethyl ether/hexane to give 3.13 (98%) of methyl 3-trifluoromethanesulfonyloxybenzoate.

(iv) methyl 3-[2-n-butyl-1-{(trimethylsilyl)ethoxymethyl}-1H-imidazol-5-yl]benzoate

To a solution of 2-n-butyl-5-tributytin-1-(trimethylsilyl)ethoxymethylimidazole (6.06 g, 11.1 mmol), methyl 3-trifluoromethanesulfonyloxybenzoate (3.13 g, 11.0 mmol) in 53 mL of 1,4-dioxane at room temperature was added tetrakis(triphenylphosphine)-palladium (0) (256 mg, 0.22 mmol). The reaction mixture was stirred under argon at room temperature for 10 minutes and then 2,6-di-t-butyl-4-methylphenol (10 mg) was added. The reaction was heated at 100°C for 3.5 hours, cooled to room temperature and treated with 70 mL of diethyl ether and 65 mL of aqueous potassium fluoride solution. The reaction mixture was left stirring at room temperature for 17 hours and then filtered through Celite®. The organic layer was washed with water and brine, dried over magnesium sulfate and concentrated in vacuo. The crude product was flash chromoatgraphed over silica gel eluting with 3:1 ethyl aetate/hexane to give 2.88 g (67%) of methyl 3-[2-n-butyl-1-{(trimethylsilyl)-ethoxymethyl}-1H-imidazol-5-yl]benzoate.

(v) methyl 3-[2-n-butyl-1-t-butoxycarbonyl-1H-imidazol-5-yl]benzoate

To a solution of methyl 3-[2-n-butyl-1-{(trimethylsilyl)ethoxymethyl}-1H-imidazol-5-yl]benzoate (2.88 g, 7.41 mmol) in 35 mL of ethanol was added 35 mL of 5N aqueous hydrochloric acid solution. The reaction mixture was heated at 55°C for 25 hours and then an additional 20 mL of 5N aqueous hydrochloric acid solution was added. The reaction mixture was heated at 70°C for one hour and then stirred at room temperature for 66 hours. The ethanol was removed in vacuo and the resulting aqueous layer was neutralized with saturated aqueous sodium bicarbonate solution and extracted with

ethyl acetate. The organic extract was dried with sodium sulfate and the solvent was removed in vacuo.

The residue (1.46 g, 5.65 mmol) was dissolved in methanol (40 mL) and was treated with triethylamine (5.2 mL, 37.3 mmol) and di-t-butyl dicarbonate (8.4 mL, 35.4 mmol) at room temperature for 42.5 hours. The mixture was concentrated in vacuo and the crude product was flash chromatographed over silica gel with a gradient of ethyl acetate in hexane (1:8 to 4:1) to give 800 mg (30%) of methyl 3-[2-n-butyl-1-t-butoxycarbonyl-1H-imidazol-5-yl]benzoate.

(vi) methyl (3-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]benzoate

To a stirred solution of trifluoromethanesulfonic anhydride (0.72 mL, 5.1 mmol) in methylene chloride (20 mL) held at -78°C under argon was added a solution of 2-chlorobenzyl alcohol (748 mg, 5.25 mmol) and diisopropylethylamine (810 mg, 6.26 mmol) in methylene chloride (25 mL). After stirring for 15 minutes at -78°C, a solution of methyl (3-[2-n-butyl-1-t-butoxycarbonyl-1H-imidazol-5-yl]benzoate (1.53 g, 4.26 mmol) in methylene chloride (10 mL) was added dropwise over 10 minutes and the mixture was stirred overnight at room temperature. A solution of 5% sodium bicarbonate solution was added with stirring and the layers were separated, washed and dried. The reaction mixture was evaporated to dryness, the residue triturated with 1:1 hexane/ethyl acetate, the solid filtered off and the filtrate was concentrated and flash chromatographed over silica gel with 1:1 hexane/ethyl acetate to provide 600 mg (38%) of methyl (3-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]benzoate.

(vii) 3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid

Methyl 3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic (600 mg, 1.63 mmol) was dissolved in 6 mL of ethanol and then 2 mL of 10% aqueous sodium hydroxide solution was added. The reaction mixture was stirred at room temperature overnight, 10% aqueous hydrochloric acid solution was added to pH 3.5 and the resulting solid was filtered, washed with water and dried to give 125 mg (21%) of 3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid as the hydrochloride salt; mp 200-202°C.

Example 2

4-[2-n-Butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic Acid

The hydrochloride salt of the title compound was prepared following the procedure of Example 1 replacing methyl 3-hydroxybenzoate with methyl 4-hydroxybenzoate; mp 238°C(d).

Example 3

3-[2-n-Butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic Acid

The hydrochloride salt of the title compound was prepared following the procedure of Example 1 replacing methyl 3-hydroxybenzoate with methyl 2-hydroxybenzoate; mp 224-226°C.

Example 4

An oral dosage form for administering orally active Formula (I) compounds is produced by screening, mixing and filling into hard gelatin capsules the ingredients in proportions, for example, as shown below.

Ingredients	Amounts
4-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]benzoic acid	100 mg
magnesium stearate	10 mg
lactose	100 mg

Example 5

The sucrose calcium sulfate dihydrate and orally active Formula (I) compounds are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

Ingredients	Amounts
3-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]benzoic acid	75 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg
talc	4 mg
stearic acid	2 mg

Example 6

4-[2-n-Butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid, 50 mg, is dispersed in 25 mL of normal saline to prepare an injectable preparation.

Example 7

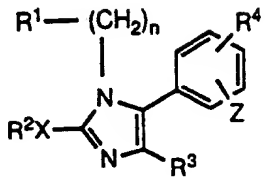
A topical opthamological solution fo. administering Formula (I) compounds is produced by mixing under sterile conditions the ingredients in proportions, for example, as shown below.

Ingredients	Amounts (mg/mL)
3-[2-n-butyl-1-{(2-chlorophenyl)-methyl}-1H-imidazol-5-yl]benzoic acid	1.0
dibasic sodium phosphate	10.4
monobasic sodium phosphate	2.4
chlorobutanol	5.0
hydroxypropanol methylcellulose	5.0
sterile water	q.s.ad 1.0mL
1.0 N sodium hydroxide	q.s.ad pH 7.4

It is to be understood that the invention is not limited to the embodiments illustrated hereabove and the right to the illustrated embodiments and all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A compound of the formula:



in which:

R^1 is adamantylmethyl, or phenyl, biphenyl, or naphthyl, with each aryl group being unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C_1-C_6alkyl, nitro, CO_2R^5, C_1-C_6alkoxy, hydroxy, SC_1-C_6alkyl, SO_2C_1-C_6alkyl, tetrazol-5-yl, SO_2NHR^5, $NHSO_2R^5$, SO_3H, $PO(OR^5)_2$, $CONR^5R^5$, CN, NR^5R^5, NR^5COH, NR^5COC_1-C_6alkyl, $NR^5CON(R^5)_2$, NR^5COW, SO_2W, or W;

R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, $(CH_2)_{0-8}$-C_{3-6}cycloalkyl, or $(CH_2)_{0-8}$phenyl unsubstituted or substituted by one to three substituents selected from C_1-C_6alkyl, nitro, Cl, Br, F, I, hydroxy, C_1-C_6alkoxy, tetrazol-5-yl, NR^5R^5, CO_2R^5, CN, $CONR^5R^5$, W, NR^5COH, NR^5COC_1-C_6-alkyl, NR^5COW, SO_2W, SO_2C_1-C_6alkyl, or SC_1-C_6alkyl;

X is a single bond, S, NR^5, or O;

n is 0-4;

R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, C_1-C_6alkyl, NR^5R^5, CO_2R^5, $CONR^5R^5$, NO_2, CN, phenyl, or W;

R^4 is CO_2R^5, $CONR^5R^5$, or tetrazol-5-yl;

Z is hydrogen, Cl, Br, F, I, C_1-C_6alkyl, C_1-C_6alkoxy, hydroxy, CN, NO_2, CO_2R^5, COR^5R^5, W,

phenyl-Y-, naphthyl-Y-, thienyl-Y-, furyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, thiazolyl-Y-, tetrazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, or isoxazolyl-Y-, with each aryl or heteroaryl group being unsubstituted or substituted by C_1-C_6alkyl, C_1-C_6alkoxy, Cl, Br, F, I, CO_2R^5, hydroxy, NO_2, CN, $CONR^5R^5$, or W;

Y is a single bond or C_1-C_6alkyl, which is straight or branched;

W is C_mF_{2m+1}, wherein m is 1-4,; and

each R^5 independently is H or C_1-C_6alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which R^1 is phenyl unsubstituted or substituted by one to three substituents selected from chloro, fluro, nitro, methyl, trifluoromethyl, methoxy, hydroxy, sulfonamido, sulfamyl, cyano, carboxy, carboC_{1-6}alkoxy, carbamoyl, or tetrazol-5-yl and n is one or two.

3. A compound according to claim 2 in which Z is hydrogen, Cl, Br, F, I, C_1-C_4alkyl, C_1-C_4alkoxy, hydrogen, CO_2H, or CO_2C_1-C_4alkyl.

4. A compound according to claim 3 in which R^2 is C_2-C_8alkyl, X is a single bond or S, and R^3 is hydrogen, chloro, fluoro, or trifluoromethyl.

5. A compound of claim 4 which is 4-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid or a pharmaceutically acceptable salt thereof.

6. A compound of claim 4 which is 3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid or a pharmaceutically acceptable salt thereof.

7. A compound of claim 4 which is 2-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a compound of claim 1 and a suitable pharmaceutical carrier.

9. A pharmaceutical composition of claim 8 wherein the compound is 4-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid.

10. A pharmaceutical composition of claim 8 wherein the compound is 3-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid.

11. A pharmaceutical composition of claim 8 wherein the compound is 2-[2-n-butyl-1-{(2-chlorophenyl)methyl}-1H-imidazol-5-yl]benzoic acid.

12. A method of antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

13. A method of treating hypertension which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

14. A method of treating congestive heart failure by administering to a subject in need thereof an effective amount of a compound of claim 1.

15. A method of treating renal failure by administering to a subject in need thereof an effective amount of a compound of claim 1.

16. A method of treating glaucoma by administering to a subject in need thereof an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/08426

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 31/415; C07D 233/64

U.S.Cl: 548/301,337,338,339,340,342,343,346; 514/386,398,399,400

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	548/301,337,338,339,340,342,343,346 514/386,398,399,400

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Structure search (Chemical Abstracts)

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Burger, A., Medicinal Chemistry, Second Edition, Interscience Publishers, Inc., New York, June 27, 1960, pp.565-571, 578-581, 600-601.	1-16
Y	EP, A, 324,377 (Carini et al.) 19 July 1989 (19.07.89) See claims 1-19, pages 226-262.	1-16

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

07 JANUARY 1992

Date of Mailing of this International Search Report

09MAR 1992

International Searching Authority

ISA/US

Signature of Authorized Officer

NGUYEN NGOC-HO
INTERNATIONAL DIVISION
LENORA A. MILTENBERGER

Form PCT/ISA/210 (second sheet) (Rev.11-87)

LW 2/22/92

I. Claim 12 drawn to a method of antagonizing angiotensin II receptors and claims 1-11 as they read on compounds embraced by Groups VI A, D, F, H.

II. Claim 13 drawn ;to a method of treating hypertension and claims 1-11 as they read on compounds embraced by groups VI A,D,F,H.

III. Claim 14 drawn to a method of treating congestive heart failure and claims 1-11 as they read on compounds embraced by groups VI A,D,F,H.

IV. Claim 15 drawn to a method of treating renal failure and claims 1-11 as they read on compounds embraced by Groups VI A,D,F,H.

V. Claims 1-11 drawn to a method of treating glaucoma and claims 1-11 as they read on compounds embraced by Groups VI A,D,F,H.

VI. Claims 1-11 drawn to products wherein:
A. when R^1 = other than tetrazolyl or phosphoryl

B. when R^1 = tetrazolyl

C. when R^1 = phosphoryl

D. when R^2 = other than tetrazolyl

E. when R^2 = tetrazolyl

F. when R^4 = other than tetrazolyl

G. when R^4 = tetrazolyl

H. when Z = other than imidazolyl, thiazolyl, tetrazolyl, triazolyl, oxazolyl, or isoxazolyl

I. when Z = imidazolyl
J. when Z = thiazolyl
K. when Z = tetrazolyl
L. when Z = triazolyl
M. when Z = oxazolyl or isoxazolyl.

VII. Claims 1-11 drawn to products embraced by Group VI B along with any of Groups VI D-M.

VIII. Claims 1-11 drawn to products embraced by Group VI C along with any of Groups VI D-M.

FURTHER INF RMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . . . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . . . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

See sheets 1-2

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

Telephone Practice

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

The various groups define products which differ in structure and element to such an extent that they are patentably distinct. A reference which anticipated but one group would not even render obvious the other groups. Separate search considerations are involved. Accordingly, lack of unity exists as the claims are not limited to a single general inventive concept.